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REVIEW ARTICLE

# Oral Cavity Carcinoma: Current Management, Controversies, and Future Directions

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## ABSTRACT

Oral cavity carcinoma (OCC) remains a major cause of morbidity and mortality in patients with head and neck cancer. Although the incidence has decreased over the last decade, outcomes remain stagnant with only a 5% improvement in overall survival in the last 20 years. Although surgical resection remains the primary treatment modality, several areas of controversy exist with regard to work-up, management of the primary and neck tumors, and adjuvant therapy. As surgical techniques evolve, so has the delivery of radiotherapy and systemic treatment, which have helped to improve the outcomes for patients with advanced disease. Recently, the addition of cetuximab has shown promise as a way to improve outcomes while minimizing toxicity, and this remains an active area of study in the adjuvant setting. Advances in microvascular free-flap reconstruction have extended the limits of resection and enabled enhanced restoration of function and cosmesis. While these advances have led to limited survival benefit, evaluation of alternative modalities has gained interest on the basis of success in other head and neck subsites. Organ preservation with definitive chemoradiotherapy, though proven in the larynx and pharynx, remains controversial in OCC. Likewise, although the association of human papillomavirus is well established in oropharyngeal carcinoma, it has not been proven in the pathogenesis or survival of OCC. Future study of the molecular biology and pathogenesis of OCC should offer additional insight into screening, treatment selection, and novel therapeutic approaches.

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## INTRODUCTION

The oral cavity is a distinct site of the head and neck region that possesses complex functional anatomy with regard to speech, swallowing, and facial projection. Anatomically, the oral cavity is composed of the mucosal lip, oral tongue, floor of mouth (FOM), mandibular and maxillary gingiva, retromolar trigone, buccal mucosa, and hard-palate subsites. Although the oropharynx is often confused as a continuous extension of the oral cavity, it is imperative to separate the two because the etiologies, management, and outcomes of cancers arising in these two head and neck sites are drastically different.

Despite advances in organ preservation and survival outcomes for oropharyngeal carcinoma (OPC) and laryngeal carcinoma, oral cavity carcinoma (OCC) remains primarily a surgical disease. In addition, despite advances in surgical techniques, adjuvant therapy, and increased understanding of the molecular mechanisms of pathogenesis, outcomes remain poor in patients with advanced cancers. This article highlights current diagnostic and treatment modalities, and explores recent advances in organ preservation, molecular targeting, and future diagnostic and therapeutic strategies.

## EPIDEMIOLOGY, STAGING, AND OUTCOMES

In 2014, 28,030 new cases of OCC were diagnosed in the United States, with 12,170 deaths occurring annually.[1] Although OCC has decreased relative to the epidemic of OPC, OCC has increased in low-risk young patients and nonsmokers.[2] Trends for human papillomavirus (HPV) –related OPC and head and neck squamous cell carcinoma (HNSCC) have remained similar, but the influence of HPV on OCC remains controversial. Squamous cell carcinoma is the most common pathologic diagnosis for oral cavity malignancies and is the main focus of this article. However, one must keep in mind that salivary gland malignancies, sarcomas, mucosal melanomas, and lymphomas can also arise within the oral cavity.

Cigarette use is the most-cited risk factor for OCC. It raises the risk of developing OCC threefold, and concomitant alcohol consumption, acting synergistically, increases the risk 10- to 15-fold.[3] Use of smokeless tobacco and betel also have high tumorigenic potential; betel quid use is highest in

South East Asia and India.[4] In addition, known genetic syndromes, such as Fanconi anemia and dyskeratosis congenita, have strong associations with the development of OCC in the absence of other known risk factors.

Overall, 5-year survival for oral cavity squamous cell carcinoma (OCSCC) is 60%, but it varies from 10% to 82% depending on stage, age, race, comorbidity, and location in the oral cavity.[5] Achieving locoregional control (LRC) in the oral tongue is particularly challenging, even in early-stage tumors, compared with other oral cavity subsites. This difficulty exists because of the lack of anatomic barriers to cancer spread, robust lymphatic drainage, and a capacity for contralateral spread. To date, data to definitively identify clinical risk factors for local recurrence are limited.[6] The presence of nodal metastases has the greatest effect on survival, reducing survival by 50%. Independent of nodal metastasis, extracapsular spread (ECS) portends worse regional and distant metastatic failure rates relative to nodal metastasis without ECS (regional recurrence, 28.9% *v* 19.2, and distant metastasis, 24.4% *v* 8.1%, respectively). This directly correlates with worse 5-year disease-specific survival (DSS) and overall survival (OS), comparing the presence of nodal metastasis with ECS relative to nodal metastasis without ECS (DSS, 48% *v* 66%, and OS, 29% *v* 51%, respectively). Although the extent of ECS is not correlated with survival, involvement of more than two lymph nodes with ECS is significantly associated with worse outcomes.[7,8] Despite recent advances in imaging, surgery, radiation, and systemic therapies, OS has improved 15% in the last 50 years but only 5% in the last 20 years. Therefore, OCC remains a major clinical challenge.[5]

The tumor, nodes, metastases, and American Joint Committee on Cancer staging systems for OCC are reliable methods for communicating about the basic characteristics and prognosis for patients with OCC (Table 1).[9] Although these staging systems have proven to be useful, additional features of OCC help in guiding treatment decisions. These include the subsite of the primary tumor; depth of invasion; the presence or absence of perineural invasion, lymphovascular invasion, and spread of tumor beyond the lymph node capsule; or ECS.

**Table 1.** Tumor, Nodes, and Metastases Classification for Oral Cavity Cancer

| Classification | Definition |
|---|---|
| Primary tumor | |
| Tx | Cannot be assessed |
| T0 | Unknown |
| T1 | < 2 cm |
| T2 | 2 to 4 cm |
| T3 | > 4 cm |
| T4a | Invades cortical bone, extrinsic tongue musculature, maxillary sinus, and/or facial skin |
| T4b | Invades masticator space, pterygoid space, and/or skull base, and/or encases the internal carotid artery |
| Regional lymph nodes | |
| Nx | Cannot be assessed |
| N0 | None |
| N1 | Ipsilateral lymph node, ≤ 3 cm in greatest dimension |
| N2a | Single ipsilateral lymph node > 3 cm and < 6 cm |
| N2b | ≥ 2 ipsilateral lymph nodes and < 6 cm in greatest dimension |
| N2c | Bilateral or contralateral lymph nodes and < 6 cm in greatest dimension |
| N3 | Any lymph node > 6 cm in greatest dimension |
| Distant metastasis | |
| Mx | Cannot be assessed |
| M0 | None |
| M1 | Any |

NOTE. Adapted from the American Joint Committee on Cancer Staging, 7th edition.[9]

## CURRENT MANAGEMENT

### *Diagnosis and Work-Up*

On initial evaluation, it is important to inquire about onset, duration, associated symptoms, risks factors, family history, and comorbidities. Physical examination remains critical for determining clinical stage to plan surgery and reconstruction, and to evaluate the need for acute interventions. Specifically, alterations in speech, articulation, and tongue mobility suggest extrinsic involvement of the tongue muscle and hypoglossal nerve; poorly fitting dentures or lose teeth may indicate alveolar bone invasion; cranial neuropathies suggest nerve invasion; and trismus is often a hallmark of pterygoid or masticator-space invasion. Palpation of the neck is imperative to clinically stage the tumor, but is not as sensitive as radiographic imaging for identifying and quantifying the burden of regional nodal disease.

Radiographic imaging is essential in the preoperative work-up to assess primary tumor extent, regional disease, and distant disease, and to identify synchronous second primary tumors. Evaluation of the head and neck most often involves high-resolution anatomic imaging. This usually is done via computed tomography (CT) with intravenous contrast material because this imaging modality is accurate and relatively inexpensive for the assessment of bone invasion as well as soft tissue extent of the primary tumor and regional nodal disease.[10] Magnetic resonance imaging (MRI) is superior for visualization of the soft tissue and hard palate and for evaluation of perineural invasion (PNI).[10] CT offers excellent specificity and positive predictive value for cortical bone invasion, whereas MRI has more false-positive results but excellent negative predictive value (NPV). Both offer high positive predictive values for positive nodes on the basis of loss of fatty hilum, central necrosis, and size. ECS can also be predicted on the basis of loss of fat planes between nodes and adjacent structures; however, its sensitivity is poor.[10] [$^{18}$F]-Fluorodeoxyglucose positron emission tomography (FDG-PET) has become widely used for detection of metastasis, second primary malignancies and post-treatment surveillance. However, use of FDG-PET in the preoperative setting for OCC remains controversial.

For detection of the primary site, no significant difference exists between use of FDG-PET, CT and/or MRI, or clinical examination.[11] In necks that are clinically node negative, or cN0, by palpation, the sensitivity of FDG-PET for identifying occult nodes is twice that of CT and MRI (41.2% *v* 21.6%, respectively).[12] One of the strongest arguments against using FDG-PET is its false-positive results with a positive predictive value of 83% and a low sensitivity for micrometastases.[13] No consensus exists in the literature regarding preoperative FDG-PET, and we know of no superiority studies or randomized control trials (RCTs) proving the benefit or cost-effectiveness for preoperative imaging with this study.

Distant metastatic work-up is critical for preoperative therapeutic decision making and prognosis. Chest radiography may be used in patients with early-stage and/or low-risk lesions and in nonsmokers. In patients with advanced stage, high-volume or N2 to 3 or matted nodes, level IV, or bilateral nodal disease, the risk of distant metastasis is higher. Therefore, chest CT or FDG-PET may be indicated.[14] No difference in sensitivity or specificity is observed between chest CT and FDG-PET in the identification of intrathoracic lung metastasis, which is the most common site of distant metastatic disease in OCC.[15]

Finally, one of the most important aspects of OCC pretreatment planning is assessment of the patient by members of a multidisciplinary oncologic treatment and rehabilitative teams. The benefits of a multidisciplinary approach are improved communication between providers, improved treatment outcomes, and enhanced enrollment of patients onto prospective clinical trials.[16] Furthermore, pretreatment dental examination facilitates dental extractions at least 2 weeks before adjuvant radiation to prevent osteoradionecrosis (ORN).[17] Pretreatment medical evaluation is imperative to understand functional status and comorbidities to help stratify patients to appropriate therapy and to further define their prognosis. Comorbidities play a critical role in outcomes, particularly in head and neck cancer because 21% of patients present with moderate-to-severe decompensation, for which severe medical decompensation is equivalent to the survival effect of a T4 or N2 tumor.[18]

### Surgical Management of the Primary Tumor

The National Comprehensive Cancer Network recommends surgery for patients with early-stage tumors and surgery or definitive concurrent chemoradiotherapy for those with advanced-staged tumors.[19] Surgery is often the first modality in sequential therapy because definitive high-dose radiation is associated with higher rates of ORN.[20-22] The goals of surgery are for complete resection of the primary tumor with negative margins and staging and treatment of regional lymphatics. Margin status is one of the most important variables associated with survival.[23-25] LRC is significantly improved with margins of 0.5 cm or greater relative to margins of less than 0.5 cm (36% *v* 18%, respectively).[23] Liao et al[26] found 0.7 cm to be the ideal distance in OCC for margin control without resecting unnecessary normal tissue. Even the outcome of intraoperative positive margins followed by immediate repeat resection revised to negative margins is associated with worse survival than negative margins achieved with initial resection (31% *v* 49%, respectively). This observation confirms the need to obtain adequate margins during initial resection.[27]

Recently, narrow band imaging and analysis of p53 mutation status of the mucosal margins has shown promise for improving the detection of tumors with histologically negative margins but positive molecular margins. However, this method remains experimental and is not being used in clinical practice because of time and cost constraints.[28,29]

Despite the well-studied quantified distances for free margins, pathologic findings of margin status can be misclassified because of tissue shrinkage, inaccurate sampling, and improper orientation. Although shrinkage is unavoidable, accurate assessment of all margins can be performed from the main specimen, as opposed to sampling from the tumor bed. A recent survey revealed a concerning lack of communication and consistency between head and neck surgeons and pathologists. Frozen sections were obtained from the main specimen by the surgeon in 32% of cases and from the tumor bed in 27%. In contrast, pathologists sampled the main specimen 40% of the time. Final margins were not correlated to location in 43% of cases and not resampled from the main specimen 37% of the time, leading to concern that margin status may be inaccurate.[30] Proper orientation of the specimen and communication with the pathologist is critical to assessing accurate margin status.

Approaches to oral cavity resection are dictated by the location and extent of invasion. The ability to obtain clear, three-dimensional margins is the most important factor in selecting the surgical approach. Lesions of the anterior or lateral oral tongue typically can be resected transorally; however, in cases with significant posterior extent and/or in patients with trismus and/or obstructive dentition, a visor flap with lingual release—sometimes referred to as a pull-through or lip-splitting incision with mandibulotomy—may be required for optimal resection. The visor flap avoids a facial incision and is associated with lower rates of oral incompetence and fistula.[31] Buccal resections can be performed with a transoral approach or with a lip-split incision to allow adequate exposure for mandibular or maxillary resection. Retromolar trigone resections often require mandibulectomy because of the posterior extent and increased rate of bone invasion. The introduction of transoral robotics surgery offers a novel approach for resecting more posterior tumors without mandibulotomy, but this remains experimental.

In many cases, FOM cancers can be resected transorally, and these excisions often involve marginal or segmental mandibulectomy. The presence of mandibular invasion is associated with worsened LRC. Mandibular resection is based on preoperative assessment of invasion of the periosteum and cortex. This type of evaluation remains a challenge because results of preoperative physical examination are predictive of only bone invasion two thirds of the time, while the addition of imaging has excellent specificity despite limitations in assessment of microscopic invasion.[10] In the management of small tumors with periosteal involvement, marginal mandibulectomy is associated with outcomes equivalent to those of segmental mandibulectomy.[32] Indications for segmental mandibulectomy are intraoperative findings of bone invasion, tooth loss with low mandibular bone height, and bone that has previously been irradiated.[32] In cases in which both a mandibulotomy and marginal mandibulectomy are performed, the risk of postirradiation ORN is unacceptably high at 71% and should be avoided. Instead, segmental mandibulectomy with osteocutaneous free-flap reconstruction is preferred.[33] Cancers of the hard palate and maxillary alveolar ridge can often be resected transorally. For larger tumors that extend into the paranasal sinuses, masticator space, or infratemporal fossa, the addition of a facial incision can improve access.

### Surgical Management of the Neck

Neck dissection is a safe procedure, but it is not without morbidity. Shoulder dysfunction, iatrogenic cranial nerve injuries, and vascular insult remain significant complications. Therapeutic neck dissection in clinically positive disease, that is, cN-positive, is a well-established treatment modality for OCC. However, the extent of dissection has evolved considerably over the past several decades. Early Halsteadian radical en bloc resections dating back to the early 1900s have largely been replaced by more selective approaches to involve only the nodal basins with expected metastasis while preserving uninvolved nonlymphatic structures. Regional control or survival rates do not decrease with more selective approaches, particularly the addition of adjuvant therapies to manage microscopic residual disease.[34] When preoperative examination reveals a cN-positive neck, this is traditionally treated with a selective neck dissection at levels I to IV or I to V. More than 75% of cases will yield positive pathologic nodes, pN-positive, and 15.8% have skip metastasis to level III or IV, without involvement of levels I or II.[34-37] Radical and modified neck dissection are no longer routinely used, but are reserved for advanced nodal disease, N3, and for disease extending into level V or invasion of critical structures in the neck.

In patients with early-stage tumors that are cN0, the decision to proceed to elective neck dissection (END) is based on a greater than 20% probability of occult nodal disease being present.[38] In this setting, END can be therapeutic if no positive nodes are identified, and it can help in determining the need for adjuvant therapy in patients found to have pN-positive disease with or without ECS.[34] In the cN0 neck, several variables are associated with occult metastasis, including the depth of tumor invasion, which has been reported to be the best predictor for regional metastasis. However, consensus regarding the extent of depth of invasion remains disputed.[39] In the oral tongue, Huang et al[40] conducted a meta-analysis to evaluate depth and identified a depth of 4 mm from the mucosal surface as the cutoff most frequently cited for END, with an NPV of 95.5%. Depth greater than 4 mm invasion is associated with increased risk of occult metastasis and late cervical recurrences.[40-42] For FOM tumors, depth of invasion greater than 1.5 mm is associated with 33% occult regional metastasis.[43] For buccal carcinomas, tumors of the maxillary alveolar ridge, and tumors of the hard palate, depth has not been extensively studied, and occult metastases are rare, occurring in 9% of patients and most often associated with T4 tumors. Therefore, END is not indicated for early-stage buccal, maxillary alveolar ridge, or hard palate cancers in cN0 cases.[36,44,45] In addition, growth type, mitosis, PNI, lymphovascular invasion, and poorly differentiated and infiltrative growth patterns are associated with metastasis. However, no clear consensus exists regarding which risk factors necessitate END.[41,45]

After the decision to proceed with END is made, the literature supports dissection of at least the supraomohyoid neck, including levels I to III. The exception is cancer of the oral tongue, for which extension to remove level IV can be considered because of the occasional identification of skip metastases, which are difficult to salvage.[37] Recently, the extent of nodal dissection to include level IIB has been questioned. Results of several prospective studies support the exclusion of level IIB because of a 3.9% incidence of positive nodes in OCC; cases involving the oral tongue have the highest rate of occult regional disease at 11.1% in cN0 cases.[46]

Alternatives to END include observation, elective radiation, or sentinel lymph node biopsy. Several prospective studies have been conducted to evaluate observation versus END, with only one study demonstrating a survival benefit with END.[39] The rate of nodal recurrence in the observation arms is 41.7% compared with 15% in the END arm. Successful salvage was higher with observation than with END (57% *v* 16%, respectively), but 66% fewer salvage attempts occurred in the END groups. Salvage neck dissection after observation often involves a more aggressive approach with added morbidity, which is what observation aims to prevent. More importantly, node-related mortality is higher with observation than with END (22% *v* 10%, respectively).[39,47]

Recently, D'Cruz et al[48] evaluated 500 patients with early-stage OCSCC who were randomly assigned to undergo END versus observation with therapeutic neck dissection to evaluate survival differences between treatment options. At 3 years, the unadjusted improvement in OS for END was 12.5% (END *v* observation with TND, 80% *v* 67.5%, respectively); this result was confirmed after the investigators adjusted for other covariates (hazard ratio [HR], 0.63; $P = .001$). No difference was observed in the cohorts when patients had pN0 disease (HR, 1.2; $P = .54$). However, among pN-positive cases, significant improvement in survival was noted in the END cohort (HR, 0.52; $P = .008$; Appendix Figs 1A to 1C, online only) The data confirmed that depth greater than 3 mm was a significant independent predictor of regional metastasis (HR, 2.17; $P = .001$). No difference was observed for OS when they compared depth less than 3 mm between the two cohorts ($P = .12$); however, the study was not powered to definitively address this issue. Overall, the study results support END for early-stage or cN0 OCSCC and confirm depth as an important variable in the decision between END or observation and therapeutic neck dissection.[48]

Sentinel lymph node biopsy (SLNB) offers a less invasive approach to more accurately identify occult metastasis in early-stage OCC. This method is based on the principle that cancer spreads first to a primary echelon lymph node that can be readily identified and meticulously evaluated for microscopic disease. This minimally invasive technique to stage the neck is well established in melanoma and breast cancer and allows for a more systematic and accurate assessment of regional metastasis without the morbidity of END.

Two multi-institutional prospective studies have been performed to assess the efficacy of SLNB in OCC. In a European trial, sentinel lymph nodes were identified in 93% of patients, with a higher NPV in the oral tongue than in the FOM (98% *v* 88%, respectively).[49] A US-based trial (ClinicalTrials.gov identifier: NCT00042926) showed that SLNB in the oral tongue had a 96% NPV overall and a 100% NPV for T1 lesions of the oral tongue. Both demonstrated improved NPV in the oral tongue relative to the FOM.[50] Recently, a meta-analysis showed a pooled NPV of 96% with early -stage tumors, yielding 98% NPV.[51] In addition, no difference was reported in regional recurrence between SLNB and END (6.7% and 6%, respectively); however, data for whether END after positive SLNB has a survival benefit are limited.[47,51] Given the accuracy and consistent NPV across most studies, SLNB offers an excellent alternative to END in the cN0 case with early OCC. This approach is widely accepted in Europe. However, its use in the United States has been limited, possibly because of the steep learning curve, the additional preoperative work-up required, and the need for an experienced multidisciplinary team. Currently, no level I evidence is available regarding survival equivalency with END.

### *Radiation*

Although definitive radiation therapy can be used for OCC, it is not routinely used because of elevated rates of ORN associated with the higher therapeutic doses required compared with doses for postoperative adjuvant therapy.[19-21] Postoperative radiation therapy (PORT) is well established for locally advanced disease, pN2 to N3 disease, PNI, ECS, and positive margins.[52,53] Despite the poor prognosis associated with these variables, the addition of PORT improved LRC and survival.[6,7,53] No RCTs have been conducted to evaluate the efficacy of PORT compared with surgery alone. However, Lundahl et al[53] performed a retrospective, matched-pair analysis to compare surgery alone versus surgery plus PORT. They found significant improvement in LRC, DSS, and OS in the PORT group.

Despite survival improvements with PORT, the potential acute and chronic effects of radiation-associated toxicity significantly influences quality of life (QoL). During the last decade, intensity-modulated radiation therapy (IMRT) has replaced standard delivery of radiotherapy, and this has improved control of radiation-associated toxicities and enhanced post-treatment QoL, particularly with regard to xerostomia.[54] Comparisons of survival outcomes have shown no difference between standard radiotherapy and IMRT.[54,55] Given the reduced toxicity and equivalent survival, IMRT has become the standard of care for PORT in OCC. More recently, intensity-modulated proton therapy (IMPT) has been tested in head and neck cancer. IMPT sharply decreases the dose of radiation distal to the planned target. Because of the theoretical reduction in dose to surrounding tissues, IMPT may reduce radiation-associated toxicity versus IMRT. Studies to compare the long-term implications of using IMPT versus IMRT on oncologic, functional, and QoL outcomes are currently underway.[56]

### Adjuvant Chemotherapy

Despite advances with surgery and PORT, disease control and OS remain challenging. In 2005, the report of two simultaneous, multicenter RCTs demonstrated the efficacy of concomitant postoperative platinum-based chemotherapy and radiation (CRT) in patients with advanced HNSCC and positive margins, multiple positive lymph nodes, or ECS. In both the EORTC 22931 trial (ClinicalTrials.gov identifier: NCT00002555) and the RTOG-9501 trial (ClinicalTrials.gov identifier: NCT00002670), patients treated with concomitant CRT had significantly improved 5-year LRC. In EORTC 22931, LRC rates were 69% in the radiation alone group versus 82% in the combined therapy group ($P = .007$), and 72% versus 82%, respectively ($P = .011$), in RTOG-9501. Rates for DFS were 36% in the radiation alone group versus 47% in the combined therapy group ($P = .04$) in EORTC 22931, and 30% versus 40%, respectively ($P = .04$), in RTOG-9501. In a pooled risk, reduction was 42% and 23%, respectively. The EORTC 22931 trial demonstrated significantly improved OS, whereas the RTOG-9501 trial did not; rates for EORTC 22931 were 40% versus 53%, respectively ($P = .02$), and 41% versus 50%, respectively ($P = .19$), for RTOG-9501. However, pooled analysis revealed a significant improvement in OS with a 28% risk reduction.[24,25] Pooled analysis demonstrated that ECS and positive margins are high-risk features that derive benefit from adjuvant CRT.[57]

Further intensification of postoperative treatment has been examined in the setting of these high-risk factors in the RTOG-0234 trial (ClinicalTrials.gov identifier: NCT00084318). The RTOG-0234 study is a phase II, randomized trial of surgery followed by chemoradiotherapy with either cisplatin plus cetuximab or docetaxel plus cetuximab for advanced HNSCC. For treatments compared with a historical cohort, the addition of cetuximab to adjuvant chemoradiotherapy was feasible, well tolerated, and improved OS. For the cisplatin arm, the HR was 0.72 ($P = .04$), and for the docetaxel arm, the HR was 0.56 ($P = .001$). DFS results were HR of 0.76 ($P = .05$) for cisplatin, and HR of 0.69 ($P = .01$) for docetaxel. A 45% reduction in distant metastasis was observed in the case of docetaxel.[58] The reduction of distant metastases with docetaxel and cetuximab is intriguing because it may represent a more effective regimen for induction of senescence in *TP53*-mutant cells compared with cisplatin.[58,59] These findings are being further evaluated in RTOG-1216 (ClinicalTrials.gov identifier: NCT01810913), a randomized, phase II and III trial of postoperative radiation plus cisplatin, docetaxel, or docetaxel plus cetuximab for high-risk HNSCC.

Although the need for adjuvant CRT has been agreed on for ECS and positive margins, the role of adjuvant radiation therapy plus either chemotherapy or molecular targeted therapy for other risk factors lacks robust level I data. Several small trials have demonstrated intermediate-risk features that improved survival with adjuvant CRT in cases involving more than two positive nodes, PNI, any lymph node greater than 3 cm or level IV or V, T4 disease, cartilage invasion, and bone invasion. These findings may be factored into treatment decisions,[52,57,60,61] and this possibility is being evaluated in the prospective, multi-institutional RTOG-0920 trial (ClinicalTrials.gov identifier: NCT00956007) to evaluate PORT with or without cetuximab for locally advanced disease.

### Reconstruction

The oral cavity is a complex site made up of several structures critical for speech, swallowing, and appearance. To be deemed successful, reconstruction should attempt to address all three, and it must be tailored to the site of the defect. Over the last 20 years, microvascular free-tissue transfer has become standard in head and neck reconstruction and has improved oncologic and functional outcomes.[62] Tongue reconstruction is critical to restoring function, and the goals of reconstruction are to allow obliteration of the oral cavity to minimize dead space, to maintain premaxillary contact for articulation and the oral phase of swallowing, and to optimize the mobility of the tip of the tongue to maximize tongue sweep.[63] Chepeha et al[63] utilized postoperative measures of tongue protrusion and elevation to identify objective targets for favorable speech and swallowing outcomes. For total glossectomy, the volume and convexity of the flap are critical to functional outcomes.[64] Mandibular reconstruction is important for speech, swallowing, and cosmesis, with functional goals of maintaining symmetric temporomandibular joint articulation to allow for mouth opening and maintenance of an occlusive plane for chewing. Cosmetic goals include providing facial height and projection to prevent the Andy Gump deformity.[65] Maxillary and hard palate reconstruction are necessary for oronasal separation and for providing a contact surface necessary for premaxillary contact and obliteration during the oral phase of swallowing. The decision between prosthetic palatal obturation and free tissue is based on the size of the defect, the location, and the number of remaining teeth.[66] In the FOM, goals of reconstruction are to separate the oral cavity from the neck and to provide soft tissue bulk between the ventral tongue and the mandible to prevent tethering of the tongue and to provide a platform for tongue elevation and protrusion. Buccal reconstruction requires adequate soft tissue to prevent cicatricial scaring and trismus. Swallowing function is well established as one of the most important factors associated with improved QoL, and oral cavity reconstruction is a critical element in restoring function after OCC resection.

### Salvage Surgery

Recurrence rates in the oral cavity are 30%, with local recurrence being the most common. Despite ease of access for surveillance and treatment, survival after salvage treatment remains poor at 30%.[67] This is the result of extensive lymphatics and a lack of physical barriers to prevent spread. In addition, the increased use of free-tissue reconstruction may mask deep recurrences. The disease-free interval between the end of initial treatment and recurrence is one of the most important factors associated with survival after salvage surgery. Liao et al[67] identified a disease-free interval cutoff of more than 10 months as being significantly associated with improved OS compared with outcomes in patients with a less than 10-month disease-free interval (54% *v* 12%, respectively; $P < .001$). For early recurrences, either surgery or chemoradiotherapy had similar outcomes; however, for late recurrences, surgical salvage was superior to chemoradiotherapy (84.4% *v* 52%, respectively).

## CONTROVERSIES

### Nonsurgical Organ-Preservation Treatment

Although surgery is the mainstay of therapy for advanced-stage OCC, success in laryngeal and OPC with nonsurgical organ-preservation therapies has prompted several investigators to explore their role in OCC.[68]

Several studies have evaluated the efficacy of definitive CRT for advanced-stage HNSCC, encompassing all head and neck subsites, and demonstrating improved survival with this modality. However, the oral cavity groups in these trials were disproportionately small, and results may been biased as a result of the favorable response of HPV-associated OPC to definitive CRT. A group from the University of Chicago extensively studied definitive CRT for OCC. In three separate studies, 5-year OS and PFS were 56% to 76% and 51% to 90%, respectively, in patients treated with definitive CRT. However 14% to 18.4% developed ORN.[20,69,70] In comparison, Gore et al[22] retrospectively studied patients treated with definitive CRT or radiation therapy and found a 5-year OS rate of 29%, a DSS rate of 30%, and an ORN rate of 36%. Surgical salvage resulted in poor outcomes. A follow-up study to compare surgery plus PORT versus definitive CRT revealed a survival benefit for surgery, with a 94% risk reduction for DSS ($P < .001$) and a 90% risk reduction for OS ($P < .001$); however, the CRT cohort had more advanced-stage tumors. To date, we know of no prospective studies in which surgery has been compared with definitive CRT. Therefore, further study is necessary to determine efficacy and equivalency.

Use of induction chemotherapy followed by surgery has been proposed to decrease the development of distant metastasis. Two prospective RCTs were performed to evaluate neoadjuvant chemotherapy versus surgery plus PORT for OCC. Licitra et al[71] evaluated resectable stage II to IV OCC with primary surgery and PORT versus induction cisplatin and fluorouracil. The study found no difference in overall survival between the group that had induction chemotherapy before surgery and the group that had surgery as the first treatment modality (5-year OS rate of 55% for both arms; $P = .767$). In addition, the rate of death associated with the induction phase of treatment was 6%. Zhong et al[72] evaluated resectable stage III or IV OCC to receive neoadjuvant cisplatin, fluorouracil, and docetaxel. No difference was observed in OS between the up-front surgical and induction chemotherapy arms (68.2% and 68.8%, respectively; $P = .918$); however, there was a nonsignificant gross improvement in distant metastatic control in the induction chemotherapy arm versus the up-front surgical arm (94.5% *v* 91.3%; $P = .674$). Given the results of these two phase III trials, induction chemotherapy followed by surgery does not seem to add a survival benefit or decrease distant metastases. However, responders seem to have improved outcomes. Although chemoselection was not a primary end point in these trials, a group from the University of Michigan recently reported a phase II trial in advanced OCC in which they specifically evaluated the ability to use induction chemotherapy to select for therapy. Patients were administered induction chemotherapy (cisplatin and fluorouracil), and, depending on tumoral response, patients were stratified to either definitive CRT for responders or salvage surgery for nonresponders. A matched analysis to a surgical cohort showed significantly better adjusted outcomes in the surgery arm compared with the induction arm; rates for OS were 65% versus 32% ($P = .03$), rates for DSS were 75% versus 46% ($P = .001$), and rates for LRC were 72% versus 26% ($P < .001$), respectively. Salvage results were poor, even in responders.[73]

Despite several studies to evaluate organ preservation, level I data suggest that induction chemotherapy has minimal benefit with regard to OS and LRC. However, it may reduce distant failure but not improve OS. Compared with definitive CRT, primary surgery has not been evaluated in adequately powered studies that permit definitive recommendations, and surgery remains the standard of care. The potential for molecular profiling to precisely identify patients who may respond to nonsurgical therapies could potentially make organ preservation a reality for select patients with OCC.

### HPV in OCC

Over the last decade, HPV has been identified as a significant causative factor in the development of OPC, with its presence being associated with improved survival. Despite clear benefits of HPV-associated OPC, its influence on OCC remains unclear. The prevalence of HPV in OCC has been reported to be between 5.9% and 21.3%. However, unlike OPC, where p16 overexpression is highly predictive of HPV infection, OCC exhibits a significant discordance between HPV-positivity and p16 expression.[74-76] Likewise, the incidence may be falsely elevated because of incorrect classification of base-of-the-tongue lesions as oral tongue lesions. Evaluation of HPV and p16 expression in OCC has failed to show any survival benefit, including in advanced OCC, where HPV-positive tumors were associated with worse survival and distant control in some studies.[74,75,77] One area of interest has been low-risk patients with oral tongue cancer. Harris et al[78] retrospectively examined patients younger than 40 years with OCC. They identified p16 overexpression in 11 (44%) of 25 patients and HPV in two (8%) of 25 patients. Although HPV may be associated with a small subset of OCC, its role in OCC remains uncertain, and no correlation seems to exist in low-risk patients.

## FUTURE DIRECTIONS: WHOLE-GENOME SEQUENCING

Two landmark publications recently used whole-genome sequencing and gene copy number analysis to study HNSCC. Known tumor suppressor genes and oncogenes were found to be mutated, including *TP53, PIK3CA, PTEN, HRAS,* and *CDKN2A*. In addition, HPV-positive tumors had a reduction in mutation rate of at least a 50% relative to smoking-associated tumors, and they were inversely correlated with *TP53* mutations, suggesting that HPV-positive tumors are genomically distinct. Of particular interest was the identification of loss-of-function mutations in *NOTCH1*, suggesting that *NOTCH* may act as a tumor suppressor gene rather than as an oncogene, as identified in other malignancies. Given these findings, HNSCC seems to have fewer targetable oncogenes for future molecular therapies.[79,80]

The Cancer Genome Atlas recently published results validating these findings. In a subset analysis of OCC, it found that reduced copy number alterations and activating mutations in *HRAS* or *PIK3CA* were associated with improved clinical outcomes. Similarly, distinct genomic difference in amplifications and deletions were observed between HPV-positive and HPV-negative tumors (Appendix Fig 2, online only).[81] The use of whole-genome sequencing has also been applied to evaluate epidemiologically distinct oral tongue cancers, specifically in young, low-risk patients compared with older, traditional patients with oral cancer. Contrary to what was identified in

HPV-positive tumors, no significant difference was found in mutation frequencies, types of mutations, or copy number between younger and older patients with oral tongue cancers. Smoking had a minimal effect on genomic changes. *FAT1* and *TP53* mutations were not significantly increased in the younger cohort and may represent a novel area of study; however, these results need to be validated.[82] The use of whole-genome sequencing has allowed clinicians to better understand the molecular mechanisms of OCC and to define genomically distinct subgroups that may be used for screening and treatment selection. Although the majority of known mutations represent nontargetable tumor suppressor genes, further study of downstream and upstream mediators may help to identify therapeutic targets.

In conclusion, despite excellent functional and survival outcomes in patients with early-stage OCC, patients with advanced-stage disease continue to have poor survival. Currently, primary definitive surgical management followed by adjuvant therapy remains the optimal therapeutic sequence with the most validated studies supporting this treatment algorithm. Nonsurgical interventions and innovations in reconstruction are active areas of clinical research in addition to complementation of standard therapy with molecular targeted therapies. Further elucidation of unique patient characteristics, phenotypically and genetically, should offer new opportunities for improved treatment selection, screening, and surveillance.

## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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## AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

**Oral Cavity Carcinoma: Current Management, Controversies, and Future Directions**

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No relationship to disclose

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## Appendix

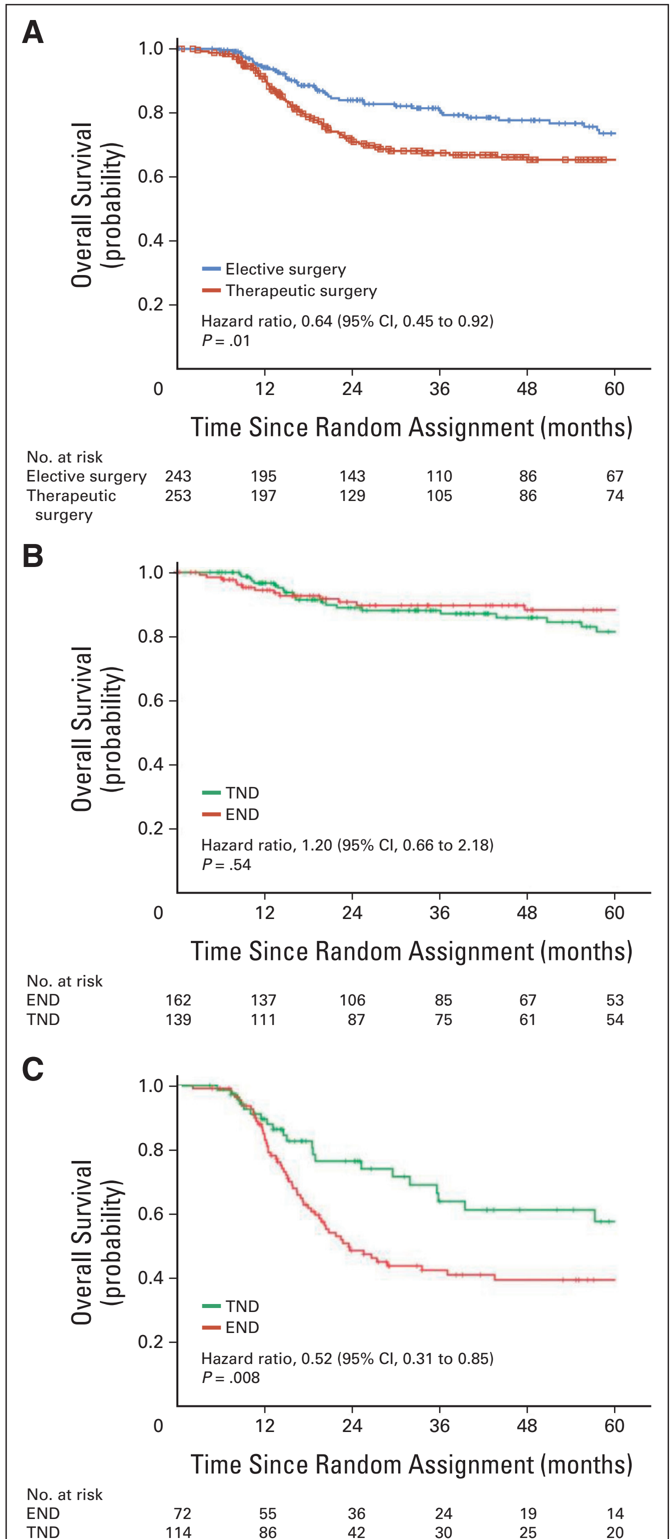


**Fig A1.** Kaplan-Meier survival curves for (A) overall survival and for pathologically (B) node-negative and (C) node-positive patients. END, elective neck dissection; TND, therapeutic neck dissection.

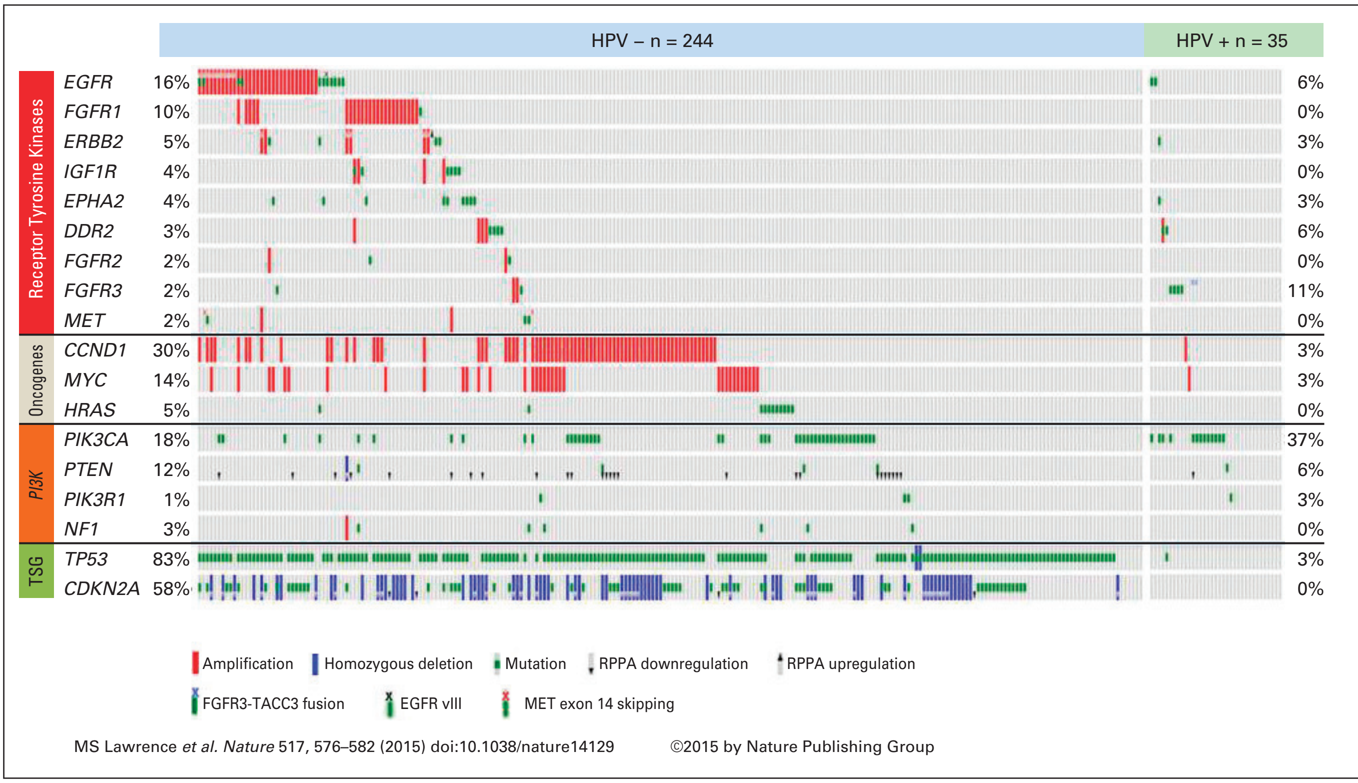


**Fig A2.** Candidate therapeutic targets and driver oncogenic events on the basis of amplification, deletions, and mutations stratified by human papillomavirus (HPV) status. Alteration events for key genes are displayed by sample (n = 279). TSG, tumor suppressor gene.